BVD: CAUSES AND CONTROL

Shollie M. Falkenberg, MS, PhD
Ruminant Disease and Immunology Research Unit, National Animal Disease Center, USDA, Agricultural Research Service, Ames, IA, USA.

BVDV GENETIC DIVERSITY, BIOTYPES, VIRULENCE AND GEOGRAPHICAL DIFFERENCES

Bovine viral diarrhea is a disease of cattle caused by one of three Pestivirus species; bovine viral diarrhea virus 1 (BVDV-1), bovine viral diarrhea virus 2 (BVDV-2) and HoBi-like virus (often referred to as BVDV-3 or bovine atypical pestivirus [1]. Recently, a proposed change of names of the Pestivirus species was presented to provide a more uniform naming system. There are 11 recognized species, A through K, where BVDV1, BVDV2, and HoBi-like virus are Pestivirus A, B, and H respectively [31]. Bovine pestiviruses belong to the family Flaviviridae, and are single-stranded, enveloped RNA viruses similar to classical swine fever virus (CSFV) in pigs and border disease virus (BDV) in sheep. Phylogenetic analysis of the three bovine pestiviruses further classified them into sub-genotypes and identified at least 21 BVDV-1 (1a–1u), three BVDV-2 and four HoBi-like subgroups [21, 32]. Bovine pestiviruses can exist as two biotypes; non-cytopathic (ncp) or cytopathic (cp). In the field, the ncp biotype has been shown to predominate, but a mutation of the persisting ncp strain can give rise to cp virus in PI animals resulting in the development of mucosal disease (MD), [4, 24]. Both ncp BVDV-1 and BVDV-2 have been isolated following outbreaks of severe acute infections associated with hemorrhagic disease; however, severe acute infections have only been reproduced under experimental conditions with ncp BVDV-2 strains [27]. Highly virulent BVDV-2 strains are the minority in the field and the majority of BVDV-2 strains are no more virulent than the BVDV-1 or HoBi-like virus strains. The understanding of virulence factors and the difference in virulence between bovine pestiviruses are not yet fully understood, but insertions have been implicated to play a role.

PATHOGENESIS

The clinical manifestation of acute BVD infections can vary and are dependent on the infecting viral strain as well as the age, immunological status and reproductive status of the animal when infected. Naïve calves and non-pregnant adult cattle acutely infected with BVD typically present with no or only minimal clinical signs such as; fever, decreased appetite and diarrhea [11]. Acute BVD infections have been shown to cause a reduction in circulating white blood cells (WBC) between 3 and 14 days after infection and are also associated with a transient depletion of lymphoid tissues [6, 7, 16]. This reduction in WBC and depletion of lymphoid tissues is associated with immune modulation that may lead to increased susceptibility of infected animals to secondary infections, such as mastitis and bovine respiratory disease complex (BRDC) [10, 13].

Acute infections of naïve dams during pregnancy can have more severe implications. The unique ability of pestiviruses to cross the placenta and infect the developing fetus has been shown to lead to a wide array of reproductive losses. The outcome of BVDV fetal infections is largely dependent on the gestational age of the fetus at the time of exposure. Early infection within approximately the first 40 day frequently leads to death of the fetus, while infection after approximately 150 days of gestation leads to transient infection (TI) which is cleared by a fetal immune response [11].

Persistent infections can only be established before the immune system is able to discriminate between self and non-self-antigens [11, 18]. This window of opportunity for persistent infection corresponds to approximately 40-125 days gestation [11, 18]. While infections during early and late gestation can still lead to economical losses, infections that lead to PI calves are a major concern due to PI animals excreting virus in most bodily fluids, throughout their lives and are, as a result, critical for the maintenance and circulation of bovine pestiviruses in the field.

TRANSMISSION

Persistently infected animals have been regarded as the major reservoir of bovine pestiviruses since they shed large quantities of virus through almost all bodily excretions and secretions, for the entirety of their lives. Other methods of transmission for bovine pestiviruses can include: animal trade (purchase of PIs or Trojan Dams), common pasturing (including cattle and domestic small ruminants), grouping of animals from different sources (such as in sale barns and feedlots), contact between domestic and wild species and other cattle management strategies that increases the likelihood of between herd contacts. Bovine pestiviruses have also been shown to spread due to indirect contact with infected animals through contaminated bedding, fomites, equipment, machinery and personnel including veterinarians [20, 22], the use of contaminated biological products such as semen, vaccines or FBS and non-bovine reservoir hosts [19]. While PI animals are considered the major source of infection in a herd, acutely infected cattle may also be a source of transmission. The length of time animals are infectious due acute infections can vary based on the health, stress level and age of the animal as well as the presence of other pathogens [3, 8, 26]. In addition, it has been reported that many non-bovine species are susceptible to infections with BVDV-1, BVDV-2 and HoBi-like pestivirus. Implications of infections in non-bovine species to cattle is an important area of research to better understand for implementation of control and eradication programs for BVD as these species could facilitate transmission of the virus in naïve populations.

CONTROL AND TESTING

The fundamental principle of any BVD control and eradication programs is to reduce the prevalence of PI animals in a population and prevent the creation of new PI animals. This can be achieved by; (a) Test-and-Cull, to identify and remove PI animals; (b) Improvements to Biosecurity, to reduce virus transmission in to a population and/or (c) Vaccination, to protect the fetus from infection and thus reduce PI development [5, 17]. The degree with which the disease is reduced is different for control compared to eradication programs [5, 12]. Control programs aim to reduce disease prevalence to a relatively low and manageable level while eradication programs aim to provide a continued absence of the disease in the population [5, 12]. Both goals, in regard to BVD, have been shown to be achievable [5, 30] and can be undertaken either at the national, regional or individual farm level. Success in either control of eradication programs for bovine pestiviruses is dependent on; effectively differentiating between animals that are susceptible to infection, undergoing acute transient infection, recovered from acute transient infection, or are PI is critical. Current diagnostic testing for bovine pestiviruses is used to identify either virus-specific antibodies (Ab), virus-specific antigen (Ag), RNA or the virus itself [28].

POTENTIAL LIMITATIONS ASSOCIATED WITH TESTING AND CONTROL

While the ultimate goal of BVD control and eradication programs are to reduce the prevalence of PI animals in a population and prevent the creation of new PI animals. The methods used for testing to identify and remove PI animals as well as vaccination as a means to reduce virus transmission in to a population and thereby reduce PI development [5], are both more so insurance plans rather than providing a 100% guarantee. As control and eradication programs are developed, variables associated with lack of detection and lack of protection should be considered. A potential variable associated lack of detection includes maternal antibodies interference in PI calves with diagnostic testing [9, 14, 15]. This interference could lead to false-negative results, a phenomenon known as “colostral diagnostic gap”. Furthermore, BVDV isolation from blood samples of PI calves is inhibited by maternal neutralizing antibodies for several weeks [2]. The colostral diagnostic gap is less pronounced to produce false-negative results when the ELISA’s is for the soluble BVDV-Erns in blood sera rather than with the NS3-capture ELISA [29]. BVDV-specific PCR with blood samples is believe to be a reliable method for testing PI animal also in the presence of colostral antibodies. For antigen capture ELISAs with skin samples, the detection of secreted soluble BVDV-Erns seems to be a most suitable, but a significant proportion of false-negatives were observed by European BVDV control programs [23, 25].

The exact reasons contributing to diagnostic failure are generally unknown, but maternal antibody interference could be one potential explanation. Other potential explanations may include the amount of virus being shed from PI animals at the time of sampling. PI calves can shed large amount of virus, but the amount of virus being shed is not constant over time and can viral titers in samples can vary over time. Another potential explanation for false-negatives is the genetic diversity associated with bovine pestiviruses. While BVDV-Erns is largely conserved, there could be point mutations causing a change in the amino acid in particular isolates that impact binding affinity, as observed with other target proteins used for diagnostics. An non-typical example of lack of detection associated with the Erns protein is in pregnant dams vaccinated with Npro and Erns double deleted mutant BVDV vaccine giving rise to PI calves due to incorporation of the vaccine virus. Given that the major skin based ELISAs are Erns based, the lack of these proteins does allow for detection of PI calves that are infected with this particular vaccine virus containing the deletion. Furthermore, inherent genetic variability in pestiviruses may play a role in detection and this could be further compounded, as genetic variability can be associated with geographical differences in pestiviruses. Additionally, the relationship between genetic and antigenic differences can be associated with lack of protection as it relates to vaccination. A clear understanding of potential reasons associated with false-negative results are needed to better implement testing programs that are responsive to limitations associated with our current diagnostic tests.

For a complete review the following papers are suggested as these papers were used to help collectively consolidate the information used in the presentation and to prepare this supplemental information.

REFERENCES:

1. Bauermann FV, Ridpath JF, Weiblen R, Flores EF (2013) HoBi-like viruses: an emerging group of pestiviruses. J Vet Diagn Invest 25:6-15
2. Brock K, Grooms D, Ridpath J, Bolin S (1998) Changes in levels of viremia in cattle persistently infected with bovine viral diarrhea virus. Journal of Veterinary Diagnostic Investigation 10:22-26
3. Castrucci G, Ferrari M, Traldi V, Tartaglione E (1992) Effects in calves of mixed infections with bovine viral diarrhea virus and several other bovine viruses. Comparative immunology, microbiology and infectious diseases 15:261-270
4. Decaro N, Lanave G, Lucente MS, Mari V, Varello K, Losurdo M, Larocca V, Bozzetta E, Cavaliere N, Martella V (2014) Mucosal disease-like syndrome in a calf persistently infected by Hobi-like pestivirus. Journal of clinical microbiology 52:2946-2954
5. Evans CA, Pinior B, Larska M, Graham D, Schweizer M, Guidarini C, Decaro N, Ridpath J, Gates MC (2019) Global knowledge gaps in the prevention and control of bovine viral diarrhoea (BVD) virus. Transboundary and emerging diseases 66:640-652
6. Falkenberg S, Johnson C, Bauermann F, McGill J, Palmer M, Sacco R, Ridpath J (2014) Changes observed in the thymus and lymph nodes 14 days after exposure to BVDV field strains of enhanced or typical virulence in neonatal calves. Veterinary immunology and immunopathology 160:70-80
7. Falkenberg SM, Bauermann FV, Ridpath JF (2017) Characterization of thymus-associated lymphoid depletion in bovine calves acutely or persistently infected with bovine viral diarrhea virus 1, bovine viral diarrhea virus 2 or HoBi-like pestivirus. Archives of virology 162:3473-3480
8. Fulton RW, Purdy C, Confer AW, Saliki J, Loan RW, Briggs RE, Burge LJ (2000) Bovine viral diarrhea viral infections in feeder calves with respiratory disease: interactions with Pasteurella spp., parainfluenza-3 virus, and bovine respiratory syncytial virus. Canadian Journal of Veterinary Research 64:151
9. Fux R, Wolf G (2012) Transient elimination of circulating bovine viral diarrhoea virus by colostral antibodies in persistently infected calves: a pitfall for BVDV-eradication programs? Veterinary microbiology 161:13-19
10. Grissett G, White B, Larson R (2015) Structured literature review of responses of cattle to viral and bacterial pathogens causing bovine respiratory disease complex. Journal of veterinary internal medicine 29:770-780
11. Grooms DL (2004) Reproductive consequences of infection with bovine viral diarrhea virus. The Veterinary clinics of North America Food animal practice 20:5-19
12. Houe H, Lindberg A, Moennig V (2006) Test strategies in bovine viral diarrhea virus control and eradication campaigns in Europe. Journal of Veterinary Diagnostic Investigation 18:427-436
13. Kapil S, Walz P, Wilkerson M, Minocha H (2005) Immunity and immunosuppression. Bovine viral diarrhea virus: diagnosis, management and control
14. Lanyon SR, Sims SK, Cockcroft PD, Reichel MP (2014) Comparison of serum, ear notches, and nasal and saliva swabs for Bovine viral diarrhea virus antigen detection in colostrum-fed persistently infected (PI) calves and non-PI calves. Journal of Veterinary Diagnostic Investigation 26:783-787
15. Lanyon SR, Reichel MP (2016) Pretreatment of serum samples to reduce interference of colostrum-derived specific antibodies with detection of Bovine viral diarrhea virus antigen by ELISA in young calves. Journal of Veterinary Diagnostic Investigation 28:345-349
16. Liebler-Tenorio EM, Ridpath JF, Neill JD (2004) Distribution of viral antigen and tissue lesions in persistent and acute infection with the homologous strain of noncytopathic bovine viral diarrhea virus. Journal of veterinary diagnostic investigation 16:388-396
17. Lindberg A, Brownlie J, Gunn G, Houe H, Moening V, Saatkamp H, Sandvik T, Valle P (2006) The control of bovine viral diarrhoea virus in Europe: today and in the future. Plurithematic issue of the Scientific and technical review, 2006, pp 961-979

18. McClurkin A, Littledike E, Cutlip R, Frank G, Coria M, Bolin S (1984) Production of cattle immunotolerant to bovine viral diarrhea virus. Canadian Journal of Comparative Medicine 48:156
19. Meyling A, Jensen AM (1988) Transmission of bovine virus diarrhoea virus (BVDV) by artificial insemination (AI) with semen from a persistently-infected bull. Veterinary Microbiology 17:97-105
20. Moen A, Sol J, Sampimon O (2005) Indication of transmission of BVDV in the absence of persistently infected (PI) animals. Preventive veterinary medicine 72:93-98
21. Neill JD, Workman AM, Hesse R, Bai J, Porter EP, Meadors B, Anderson J, Bayles DO, Falkenberg SM (2019) Identification of BVDV2b and 2c subgenotypes in the United States: Genetic and antigenic characterization. Virology 528:19-29
22. Niskanen R, Lindberg A (2003) Transmission of bovine viral diarrhoea virus by unhygienic vaccination procedures, ambient air, and from contaminated pens. The Veterinary Journal 165:125-130
23. Oettl J, Schöpf K, Matt M, Dünser M, Auer G, Wolf G, Brem G (2010) Progress in the eradication of bovine virus diarrhoea (BVD) using tissue samples and blood tests in the state of Tyrol. Wiener Tierärztliche Monatsschrift 97:203-209
24. Peterhans E, Bachofen C, Stalder H, Schweizer M (2010) Cytopathic bovine viral diarrhea viruses (BVDV): emerging pestiviruses doomed to extinction. Veterinary research 41:44
25. Presi P, Struchen R, Knight-Jones T, Scholl S, Heim D (2011) Bovine viral diarrhea (BVD) eradication in Switzerland—experiences of the first two years. Preventive veterinary medicine 99:112-121
26. Richer L, Marois P, Lamontagne L (1988) Association of bovine viral diarrhea virus with multiple viral infections in bovine respiratory disease outbreaks. The Canadian Veterinary Journal 29:713
27. Ridpath JF, Falkenberg SM, Bauermann FV, VanderLey BL, Do Y, Flores EF, Rodman DM, Neill JD (2013) Comparison of acute infection of calves exposed to a high-virulence or low-virulence bovine viral diarrhea virus or a HoBi-like virus. American journal of veterinary research 74:438-442
28. Saliki JT, Dubovi EJ (2004) Laboratory diagnosis of bovine viral diarrhea virus infections. The Veterinary clinics of North America Food animal practice 20:69-83
29. Sandvik T (2005) Selection and use of laboratory diagnostic assays in BVD control programmes. Preventive veterinary medicine 72:3-16
30. Scharnböck B, Roch F-F, Richter V, Funke C, Firth CL, Obritzhauser W, Baumgartner W, Käsbohrer A, Pinior B (2018) A meta-analysis of bovine viral diarrhoea virus (BVDV) prevalences in the global cattle population. Scientific reports 8:14420
31. Simmonds P, Becher P, Bukh J, Gould EA, Meyers G, Monath T, Muerhoff S, Pletnev A, Rico-Hesse R, Smith DB (2017) ICTV virus taxonomy profile: Flaviviridae. Journal of General Virology 98:2-3
32. Yeşilbağ K, Alpay G, Becher P (2017) Variability and global distribution of subgenotypes of bovine viral diarrhea virus. Viruses 9:128